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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,765	08/09/2001	Michael J. Mahan	220002060723	6765

25226 7590 11/20/2003

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EXAMINER	
FIELD, TAMMY K	
ART UNIT	PAPER NUMBER
1645	17

DATE MAILED: 11/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,765	MAHAN ET AL.	
	Examiner	Art Unit	
	Tammy K. Field	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26 and 31-34* is/are pending in the application.

4a) Of the above claim(s) *8-13, 23-26, and 31-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 14-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6 and 8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Priority

1. Applicant's claim for domestic priority of U.S. Patent Application Ser. No. 09/241,951, converted to U.S. Provisional Ser. No. 60/183,043, and 09/305,603, converted to U.S. Provisional Ser. No. 60/198,250 under 35 U.S.C. 119(e) is acknowledged. Applicant is required to provide updated status of all parent applications.

Information Disclosure Statement

2. The information disclosure statements received May 16, 2002 and July 12, 2002 have been considered. Initialed copies are enclosed.

Election/Restrictions

3. Applicant's election with traverse of the Invention of Group I in Paper No. 10 is acknowledged. The traversal is on the ground(s) that the characterization of Invention I as comprising " a bacterium with a mutation in the DNA adenine methylase gene is through applicants submission, a "bacteria with altered DNA adenine methylase activity" and that a bacterium rendered non-pathogenic as a result of altered DAM activity is specified in the claims which may or may not be a representative embodiment of bacteria with "altered DNA adenine methylase activity which renders the bacteria non-pathogenic. Applicants' point that a mutation is not required for altered DNA adenine methylase activity which renders the bacteria non-pathogenic is respectively acknowledged, but this is not found persuasive because applicant

hasn't explained why restriction is improper. Further, species traversal is noted, but each of the species listed are different organisms and therefore, one organism is not obvious over the other.

The requirement is still deemed proper and is therefore made FINAL.

4. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product

claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

5. Claims 8-13, 23-26, and 31-34 are drawn to non-elected Invention II and of species of Invention I of Group I. Claims 1-7, and 14-22 are presently under examination.

Claim Objections

6. Claim 1 is objected to because of the following informalities: Placing a comma after the word activity or amending the word which to recite "wherein the" will help make the claim language clear.

Appropriate correction is required.

Claim Rejections - 35 USC § 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an

international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

7. Claims 1-7, 14-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Miller, III, *et al.* (US Patent No. 5,731,196, published March 24, 1998).

Claims are drawn to a composition comprising a pharmaceutically acceptable excipient, adjuvant and Salmonellae bacterium with altered DNA adenine methylase activity wherein the altered DNA adenine methylase (Dam) activity renders the bacterium non-pathogenic by an artificially engineered change in the bacterium's genome by deletion, an insertion, and a mutation of a native sequence. Further dependent claims of claim 1 are drawn to a bacterium altered by a heterologous nucleotide operatively inserted into a plasmid of said bacterium. Claim 15 and subsequent dependent claims are drawn to an immunogenic composition comprising a pharmaceutically acceptable excipient and live bacterium comprising altered Dam activity reducing virulence relative to the bacteria with wild-type Dam activity. Further claims are drawn to an attenuated strain of a pathogenic bacterium containing a mutation that alters Dam activity such that bacterium is attenuated.

The evidence of record discloses in applicants' Provisional Applications; 60/183,043 at page 21, line16 – page 22, line 14 and 60/198,250 at page 21, line 16 – page 22, line 20. The specification of both Provisional Applications disclose that "Salmonella pathogenesis is known to be controlled by PhoP, a DNA binding protein". Results of regulatory studies disclosed by applicants further disclose that both "DAM and PhoP constitute an overlapping global regulatory network controlling Salmonella virulence". Since there is a close overlapping relationship

between PhoP and DAM regulatory genes, inherently alterations of the Salmonella genome affecting virulence in PhoP are anticipated in the instant invention.

Miller, III *et al.* teach in preferred embodiments a bacterial cell, *e.g. S. typhi* including a virulence attenuating mutation in a gene regulated by a phoP regulatory system (instant Claims 1-7) in a vaccine composition at column 2, line 52 – column 3, line 51. Miller, III *et al.* further teach a mutation attenuates virulence if, as a result of the mutation, the level of virulence of the mutant cell is decreased in comparison with the level of parent strain (instant Claim 19) at column 5, lines 57-60. Miller, III *et al.* also teach a live Salmonella vaccine, as used herein, is a preparation including material that evokes a desired biological response, *e.g.* an immune response, in combination with a suitable carrier (instant Claims 1-7, 14, and 15-18) at column 5, line 39.

Inherently Miller, III *et al.* anticipates the now claimed invention. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir 1999) states, "Artisans of ordinary skill may not recognize the inherent characteristics of functioning of the prior art....However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discover". The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

Miller, III *et al.* thus anticipates the instantly claimed invention.

8. Claims 1-7, 14-18, and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Miller *et al.* (US Patent No. 5,843,426, published December 1, 1998).

Miller *et al.* teach a Salmonella vaccine, the invention features a bacterial cell, preferably a Salmonella cell, e.g. *S. typhi* (instant Claims 6-7) the virulence of which is attenuated by a first mutation in a phoP region (instant Claims 1- 5), where said bacterial cell can be used as a vaccine to immunize a mammal against salmonellosis (instant Claims 14-18) at column 2, line 65 – column 3, line 11. Miller *et al.* also teach that constitutive expression of phoP (instant Claim 22) is the result of a change or mutation in the phoP regulatory region at column 3, lines 35-41.

The reference thus anticipates the instantly claimed invention.

9. Claims 1-7, 14-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Miller, S.I. and Mekalanos, J.J. 1990. (J. Bacterio. 172(5): 2485-2490).

Claims are drawn to a composition comprising a pharmaceutically acceptable excipient, adjuvant and Salmonella bacterium with altered DNA adenine methylase activity wherein the altered DNA adenine methylase (Dam) activity renders the bacterium non-pathogenic by an artificially engineered change in the bacterium's genome by deletion, an insertion, and a mutation of a native sequence. Further dependent claims of claim 1 are drawn to a bacterium altered by a heterologous nucleotide operatively inserted into a plasmid of said bacterium. Claim 15 and subsequent dependent claims are drawn to an immunogenic composition comprising a pharmaceutically acceptable excipient and live bacterium comprising altered Dam activity reducing virulence relative to the bacteria with wild-type Dam activity. Further claims are drawn to an attenuated strain of a pathogenic bacterium containing a mutation that alters Dam activity such that bacterium is attenuated.

Miller, S.I. and Mekalanos, J.J. teach a composition comprising a pharmaceutically acceptable excipient and attenuated *S. typhimurium* at pages 2485-2486 (also see Table 1). Miller, S.I. and Mekalanos, J.J. also teach attenuated *S. typhimurium* is an immunogenic composition when mice previously used for live vaccine inoculation of attenuated *S. typhimurium* survived oral challenge experiments at page 2486 at Table 2. Miller, S.I. and Mekalanos, J.J. further teach a phoP locus mutation (pho-24) results in constitutive expression of genes activated by the PhoP-PhoQ two-component regulatory system and in attenuation of virulence and survival within cultured macrophages at 2488, Figure 3. Miller, S.I. and Mekalanos, J.J. incorporate thought reference, Miller, S.I. et al. 1989 Proc. Natl. Acad. Sci. USA 86: 5054-5058 that null mutations in phoP and phoQ decrease the expression of the same genes whose expression is derepressed by the pho-24 mutation and it is apparent that mutations that inactivate or activate the PhoP-PhoQ regulation can attenuate virulence at page 3488.

The reference thus anticipates the instantly claimed invention.

Since the office does not have the facilities for examining and comparing applicants' detection and diagnosis methods with the methods disclosed in the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed method and the methods of the prior art (*i.e.* that the methods of the prior art does not possess the same material structural and functional characteristics of the claimed methods). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald *et al.*, 205 USPQ 594.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-7 and 14-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-46 of copending Application No. 09/928,227 (Pregrant Publication 2002/0086332 A1).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and the copending application ('227) are both drawn to a composition of bacteria with altered DNA adenine methylase (Dam) activity.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 1-7 and 14-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of copending Application No. 09/927,788 (Pregrant Publication 2002/0081317 A1).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and the copending application ('788) are both drawn to an immunogenic composition of bacteria with altered DNA adenine methylase (Dam) activity by a heterologous nucleotide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. The prior art of record and not relied upon is considered pertinent to applicant's disclosure:

a. Curtiss, III et al. US Patent No. 5,424,065, published June 13, 1995. Vaccines containing avirulent PHOP-Type microorganisms.

b. Groisman, E.A. and Heffron. 1995. *In*: Two-component signal trasduction. James A. Hoch and Thomas J. Silhavy, eds. ASM Press, Washington, D.C. Pages 319-332.

c. Mahan, M.J. et al. 1993. Selection of bacterial virulence genes that are specifically induced in the host tissue. Science v259 (5059): 686-689.

Status of the Claims

13. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tammy K. Field whose telephone number is (703) 305-4447. The examiner can normally be reached on Monday-Friday from 7am-4: 30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909.

Papers relating to this application may be submitted to Technology Center 1600 Group 1640 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The fax phone number for the

organization where this application or proceeding is assigned is (703) 872-9306 for regular communications and After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Tammy K. Field
November 14, 2003

MARK NAVARRO
PRIMARY EXAMINER